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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,394	07/28/1999	CHONG-JIN OON	56972/JPW/AK	6815

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EXAMINER
WORTMAN, DONNA C

ART UNIT	PAPER NUMBER
1648	21

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/362,394	OON ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 19-36 and 38-68 were canceled and claims 69-105 were added in Paper No. 20. Claims 69-80, 82, and 83 are drawn to oligonucleotides linked to a fluorescent dye at the 5' terminus. Claim 81 is drawn to an oligonucleotide linked to a biotin at the 5' terminus. Claim 84 is drawn to a composition comprising two oligonucleotides, one linked to a fluorescent dye at the 5' terminus and one linked to a biotin group at the 5' terminus. Claims 85-95 are drawn to a method for identifying a human hepatitis B virus surface antigen mutant 145 using specifically recited primers. Claims 96-105 are drawn to a method for identifying a wildtype human hepatitis B surface antigen using specifically recited primers.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85, 87-92, 94 and 95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 85 recites a method for identifying a human hepatitis B virus surface antigen mutant 145 comprising several steps, including contacting an immobilized third oligonucleotide that comprises a mutation present in a mutant human hepatitis B virus in step (D)(i). The mutation in step (D)(i) must necessarily be present at the amino acid at position 145 of human hepatitis B surface antigen in order that the method work as claimed, since detecting that mutation is the purpose of the method and since the hybridization between the single stranded

nucleic acid which comprises the fluorescent dye and the immobilized third oligonucleotide identifies the sample as one containing a human hepatitis B virus surface antigen mutant 145, and since the specification does not teach any other kind of "third oligonucleotide" that would work to detect the mutation. This rejection might be overcome if Applicant were to incorporate the limitations of claim 86 into claim 85 as presently recited.

Claims 69-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/40193 to Stuyver et al. in view of Guo et al. (Nucleic Acids Research 22(24):5456-5465, 1994, and of US Patent 6,100,030 to McCasky Feazel et al., all of record, essentially for reasons of record in rejecting claims 19-36 and 38-68 in the previous Office action. In particular, Stuyver et al. teach a method for detection of mutant HBV sequences in a sample comprising using primers, if necessary, to amplify the region(s) bearing mutations of interest and using appropriate specific probes, preferably about 10-25 nucleotides long, corresponding to the region bearing the mutation and its wild-type counterpart for hybridizing to the nucleic acids that are in the sample or are amplified from the sample. Fig. 1 presents nucleotide sequences for a number of HBV strains; sheet 4 of Fig. 1, e.g., discloses the nucleotide sequences that encode HBsAg and indicates the location of codon 145. Stuyver discloses solid supports, including beads or chips, for immobilizing oligonucleotide probes, and also discloses that the oligonucleotides may be modified in order to facilitate immobilization or in order to improve hybridization. Such modifications include homopolymer tailing, coupling with reactive groups, or coupling to substances such as biotin.

Oligonucleotides to be used as primers or probes may also be labeled. See, e.g., page 16, lines 5-20. Table 1, page 28 indicates examples of HBsAg primers (SEQ ID NO's 75, 76, 94, 104, 105) and probes for HBsAg codon 145 wild type and mutant sequences (SEQ ID NO's 77-82). Stuyver differs from the instant invention only in not disclosing specific fluorescent labels for the primers and probes, in not specifically disclosing a "C 7 primary amine" for immobilizing probes, and in not disclosing primers and probes identical in sequence to those instantly claimed. With respect to particular labels for primers used in amplification of sequences intended for later hybridization for genetic analysis, Guo et al. disclose DNA amplification using a set of primers, one of which has 5' biotin and one of which has a fluorescent label, fluorescein, where the biotin is to be used to separate the strands using streptavidin-coupled magnetic beads (see page 5457, DNA amplification and strand separation). Guo et al. also disclose hybridization sequences having polydT spacers and an aliphatic amino group at the 5' terminus (see, e.g., Fig. 1 and Table 1) to facilitate immobilization on glass supports. Neither Guo nor Stuyver specifically disclose an assay format involving two different fluorescent labels. McCasky Feazel et al. provide extensive background information regarding oligonucleotide hybridization assay formats, including those in which two different fluorescent labels are used, one on the 5' end of the amplified product and one on the 5' end of the immobilized probe. See, e.g., col. 23, lines 36-53 and col. 30, line 7-col. 31, line 34, listing, *inter alia*, Texas red and fluorescein derivatives as conventional and widely known fluorescent labels, where the two labels are chosen to have appropriate characteristics. While the HBV primers and probes specifically disclosed by Stuyver

are not identical to those instantly claimed, it would have been obvious to one of ordinary skill in the art to have selected other, similar, HBsAg primers and probes that include relevant portions of HBsAg in order to amplify the region including codon 145 and the sequences that encode the wild type and the escape mutant codon 145, based on the extensive teachings of Stuyver, and to have successfully detected the mutation of interest, using the conventional formats and labels whose details are taught by Guo et al. and McCasky Feazel et al., because Stuyver teaches the importance of detecting HBV codon 145 mutations and teaches that amplification of viral nucleic acid by PCR and hybridization with immobilized probes, whose details are taught by Guo et al. and McCasky Feazel et al., are conventional methods for amplification and detection of specific sequences of interest.

Applicant has argued (1) that the cited references fail to teach or suggest all elements of the rejected claims, and specifically, Applicant asserts that the oligonucleotide sequences as now recited are not taught; (2) that the Examiner has used impermissible hindsight; and (3) that the cited references do not teach that particular oligonucleotide sequences would be obvious to combine with specific fluorescent labels and C-7 amines.

The arguments have been considered but not found persuasive. With respect to point (1), it is noted that the rejection of record was made under 35 USC 103, not under 35 USC 102, and that, while Stuyver does not teach the identical probes and primers, Stuyver recognizes the importance of detecting escape mutants, including a mutation at amino acid 145, and provides ample guidance for selecting probes and primers that

would work to do so. With respect to point (2), in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It is apparent from the availability of the references cited that selection and labeling of probes and primers to identify human hepatitis B surface wildtype antigen and antigen mutant 145 only takes into account knowledge which was within the level of ordinary skill at the time the claimed invention was made. With respect to point (3), in the absence of evidence to the contrary, one would reasonably have expected to be able to label, immobilize, and successfully use primers and probes selected using the teachings of Stuyver et al., using the conventional labels and formats as taught by Guo et al. and McCasky Feazel et al., to identify human hepatitis B surface wildtype or mutant antigen as claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
March 12, 2003